UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/735,180	12/12/2003	Larry Norton	93580.010100	2583

32361 7590 11/07/2007

GREENBERG TRAURIG, LLP
MET LIFE BUILDING
200 PARK AVENUE
NEW YORK, NY 10166

EXAMINER	
OLSON, ERIC	
ART UNIT	**PAPER NUMBER**
1623	

NOTIFICATION DATE	DELIVERY MODE
11/07/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

SchindlerB@gtlaw.com
LucasCh@gtlaw.com
NYIPmail@gtlaw.com

Office Action Summary	Application No.	Applicant(s)	
	10/735,180	NORTON, LARRY	
	Examiner	Art Unit	
	Eric S. Olson	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 September 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-43,45-69,71-82 and 119-128* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-43,45-69,71-82 and 119-128* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

This office action is a response to applicant's communication submitted September 14, 2007 wherein the arguments of record in the previous office action are traversed. This application claims benefit of provisional application 60/432840, filed December 12, 2002.

Claims 40-43, 45-69, 71-82, and 119-128 are pending in this application.

Claims 40-43, 45-69, 71-82, and 119-128 as amended are examined on the merits herein.

The following rejections of record in the previous office action are maintained:

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 40-43, 45-69, 71-82, and 119-128 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hudis et. al. '99 (Reference included with PTO-1449, titled "Sequential Dose-Dense Doxorubicin, Paclitaxel, and Cyclophosphamide for Resectable High-Risk Breast Cancer :Feasibility and Efficacy", Journal of Clinical oncology (1999) Vol. 17, No. 1, pp. 93-100), in view of Henderson et al. (reference of record in previous office action) in view of Winer et al. (Reference included with PTO-

1449, marked as reference B by examiner) Hudis et. al. '99 describes a course of sequential dose-dense chemotherapy using the same three drugs specified by the claimed invention. In particular, p. 95, Fig. 1 illustrates the course of treatment used, which consisted of three doses of Doxorubicin, separated by 2 weeks (14 days) each, three doses of Paclitaxel separated by 2 weeks each, and three doses of cyclophosphamide separated by 2 weeks each. The same course of treatment is described on p. 94 right column, under the heading *Treatment Plan*. Furthermore, the same paragraph mentioned above (p. 94, left column, *Treatment Plan.*) also discloses that, "All nine cycles of chemotherapy were supported by granulocyte colony stimulating factor, 5 μg/kg subcutaneously, administered on days 3 through 10." Hudis et al. '99 discusses the strategy of dose escalation and determines that dose densification is a superior strategy to dose escalation for improving the effectiveness of chemotherapy. (p. 94, left column, paragraphs 3-4) In addition, Hudis et al. discusses the relatively high doses of the drugs used and concludes that there is no evidence that the doses used were actually superior to lower doses of 60, 600, and 175 mg/m^2 for doxorubicin, cyclophosphamide, and paclitaxel, respectively. (p. 97, paragraph 2 – p. 98, paragraph 1) Hudis et al. '99 does not teach the specific doses of 60, 175, and 600 mg/m^2 for doxorubicin, paclitaxel, and cyclophosphamide mentioned in the aforementioned claims, nor does Hudis et. al. teach the administration of said chemotherapy agents in four cycles or in an order other than doxorubicin first, paclitaxel second, and cyclophosphamide third.

Henderson et al. describes a study (CALGB 9344) comparing several chemotherapy regimens involving Doxorubicin, Paclitaxel, and Cyclophosphamide. These drugs were administered in amounts of 60, 75, and 600 mg/m^2 in four cycles each. Furthermore, the study concluded that escalation of the dose of doxorubicin produced no additional benefit.

Winer et al. discloses a study of dose intensification of paclitaxel. Doses of 175, 210, and 250 mg/m^2 were compared and it was determined that the higher doses showed no improvement in response or survival over 175 mg/m^2. Although the time to progression was longer, this benefit was offset by the greater toxicity at the higher doses.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the teaching of Hudis et. al. '99 by reducing the dosage of the drugs used and increasing the number of cycles in each treatment, as well as by administering the three drugs in the various orders disclosed in instant claims 120-125.

One of ordinary skill in the art would have been motivated to do so in order to avoid administering an excess of these toxic drugs by reducing the dose and to ensure complete eradication of cancer cells by adding a fourth cycle to each treatment, particularly in view of the teaching of Henderson et al. and Winer et al. disclosing that lower doses of these drugs are equally effective. One of ordinary skill in the art would have been motivated to administer the drugs in a different order because the neither Hudis et al. '99 nor any other prior art discloses any reason to believe that the order in which the drugs are administered in a dose-dense regimen affects the treatment

outcome. In particular, because the different drugs are considered to act on different selectively sensitive sub-populations, it should not matter which sub-population is eradicated first by the chemotherapy regimen as each sub-population is only significantly affected by one particular phase of the sequential treatment.

One of ordinary skill in the art would have reasonably expected success because the reduced doses and increased number of cycles were already known to be effective for the treatment of breast cancer, and because the treatment regimen of the instant invention differs only slightly from that of Hudis et al. '99. Furthermore, determination of exact treatment regimens, including exact dosage, duration of treatment, and order of administration of various drugs, is within the ordinary skill in the practice of medicine.

Although Henderson et al. and Winer et al disclose a non-dose-dense protocol, the specific dosages used by these references can be applied to a dose-dense protocol with a reasonable expectation of success because the differences observed between dose-dense and non-dose-dense protocols are not the result of any changes in the dose-response curve of the drugs used but rather the result of the same drug, producing the same cell kill percentage, being used more often. In fact, the theoretical rationale for dose-dense chemotherapy, disclosed on p. 93, left column, second paragraph of Hudis et al. '99, rests on the knowledge that, "In these laboratory models, anticancer drugs kill a fraction of cells (called log-kill) and this is constant regardless of the number of cells present when the drugs are administered." This statement assumes that the dose-response curve, and thus the percentage of cells killed at a given dose, does not change based on the interval between treatments. Thus the disclosure in the

prior art of a particular dose of a chemotherapeutic drug used in a chemotherapy method provides a clear rationale for using the same dose in a dose-dense protocol with the expectation that the efficacy will be the same as it is in the non-dose-dense protocol.

Although Henderson et al. and Winer et al. do not examine the effect of dose escalation of cyclophosphamide on the effectiveness of these drugs, the mere fact 600 mg/m^2 was used with a reasonable measure of success by Henderson et al. provides a motivation and reasonable expectation of success for one of ordinary skill in the art to use this dose.

Furthermore, as stated by Applicant in the amendment submitted August 11, 2006, "the establishment of a dose-response curve, for a particular chemotherapeutic agent, against a particular cancer, is part of the **routine experimentation** that takes place in the field of oncology," and, "the experimentation required to arrive at an optimal dose, for a particular chemotherapeutic agent, against a particular cancer, is **absolutely routine** in the field of oncology." Even assuming, for the sake of argument, that Hudis et al. '99 is considered on its own merits, without the additional teaching of Henderson et al., modifying the specific dosage levels disclosed by Hudis et al. '99 and discovering that the lower dosages disclosed in the instant claims are equally effective is, by Applicant's own reasoning, merely routine and ordinary experimentation which is therefore obvious over the prior art. Therefore, although Henderson et al. has been cited to demonstrate that lower doses of the disclosed chemotherapeutic agents were

known in the art at the time of the invention, Henderson et al. is not necessary to repair the defect in the teaching of Hudis et al. '99 and render the instant claims obvious.

Therefore the invention taken as a whole is *prima facie* obvious.

Response to Argument:

Applicant's arguments submitted September 14, 2007 have been fully considered as applied to the above rejection and have not been found to be persuasive to overcome the rejection of the instant claims under 35 USC 103.

Applicant asserts that the references teach away from their combination. Specifically, it is claimed that the Hudis et al. '99 reference discloses that there "may be a small additional benefit" to using doses of paclitaxel over 175 mg/m^2, and that the high doses used in the disclosed study were chosen because there was no confirmation that lower doses would be equivalent to higher doses. These observations do not teach or suggest that lower doses are inferior, but merely that the authors of the Hudis et al. '99 reference did not know whether or not they were equivalent. This is not a "teaching away" so much as a "failure to teach toward" the claimed invention. The uncertain, equivocal teachings of Hudis et al. '99 (which was concerned with dosage frequency and sequence, not dose intensity) as regards the optimal dose intensity would not lead one of ordinary skill in the art away from the clear teachings of Henderson and Winer, which are in fact concerned with finding the optimal does intensity. One of ordinary skill in the art would not see the teaching of Hudis et al. '99 as a positive recommendation of a high dose of chemotherapy agents but as a failure to recommend any specific dose intensity.

Applicant also argues that Hudis et al. '99 teaches away from combining the cited reference because the reference states that dose-dense treatment with escalated doses is feasible and associated with a promising disease-free survival. However, as noted above, this reference does not actually compare escalated doses to conventional doses. The decision to use escalated doses was an arbitrary one made in the face of uncertain data as to the optimal dose. In order to teach away from combining the references, Hudis et al. '99 would actually need to give some positive reason to believe that lower doses would be inferior to the escalated doses used in the disclosed clinical trial.

Finally, Applicant argues that Hudis et al. '99 does not consider dose densification to be a superior alternative to dose escalation. However, p. 94, left column, paragraph 4 of the reference, explicitly contrasts the two approaches and states that increased dose density should improve outcomes even if the dose-response relationship for dose escalation is not rising sharply at the doses used. (i.e. if the dose escalation has reached the point of diminishing returns)

In conclusion, in order for a reference to teach away from its combination with another reference it must disclose information that would lead one of ordinary skill in the art to believe that combining it with the secondary reference would be disadvantageous. In the instant case, Hudis et al. '99 states that dose intensification reaches a point of diminishing returns, and indicates that there is no clear, unequivocal data to support the relatively high doses of chemotherapeutic agents used. This is not a teaching away

from lowering the doses in view of another reference that teaches that the lower doses are equally effective.

For these reasons the rejection is deemed proper and made **FINAL**.

Conclusion

No claims are allowed in this application. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Eric Olson
Patent Examiner
AU 1623
10/31/07

Anna Jiang
10/31/07
Supervisory Patent Examiner
AU 1623